Therapy with ticagrelor/prasugrel is associated with enhanced fibrinolysis and suppressed platelet activation as compared to clopidogrel in chronic coronary syndrome

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INTRODUCTION

Enhanced platelet activation and impaired fibrinolysis contribute to cardiovascular events in coronary artery disease (CAD) [1, 2]. Dual antiplatelet therapy (DAPT) is the cornerstone of pharmacotherapy following percutaneous interventions (PCI) in CAD [3]. Ticagrelor and prasugrel are recommended as part of DAPT in acute coronary syndrome (ACS), while acetylsalicylic acid (ASA) combined with clopidogrel remains the standard treatment in chronic coronary syndrome (CCS) [3, 4]. Based on expert opinions, the use of ASA and ticagrelor/prasugrel may be considered in CCS patients with very high ischemic risk [3].

Ticagrelor and prasugrel have been shown to reduce circulating platelet activation markers in ACS [5]. Data on drug-induced alterations to platelet markers in CCS are scarce [6].

Plasminogen activator inhibitor-1 (PAI-1), the main inhibitor of fibrinolysis, is associated with the severity of CAD, including the risk of ACS, stroke, in-stent thrombosis, and restenosis [2]. Little is known about the impact of $P2Y_{12}$ inhibitors on plasma PAI-1 in CCS.

We investigated whether addition of ticagrelor or prasugrel to ASA can improve fibrinolysis via reduction of PAI-1 in association with suppressed platelet activation in CCS.

METHODS

Patients

Between July 2020 and September 2021, we enrolled patients with CCS (class II or III angina according to the Canadian Cardiovascular Society) and at least one angiographically significant coronary lesion of a major epicardial vessel (≥50% diameter stenosis). We excluded patients with recent ACS or stroke (up to three months) or PCI (up to one month), acute infection, severe comorbidities including active malignancy, advanced liver or kidney disease, and those on anticoagulation. We collected data on comorbidities, using definitions previously described [7]. The study protocol was approved by the Jagiellonian University Medical College Ethics Committee. Study participants provided informed written consent.

Laboratory measurements

In fasting blood samples collected between 8:00 and 10:00 AM, basic laboratory parameters were determined. Immunoenzymatic assays were used to measure plasma soluble CD40 ligand (sCD40L, EIAab, Wuhan, China), P-selectin (R&D Systems, Minneapolis, MN, US), platelet factor 4 (PF4, R&D Systems), and PAI-1 antigen (Hyphen Biomed, Neuville-sur-Oise, France).

Statistical analysis

Continuous variables were reported as medians (interquartile ranges [IQR]). The Shapiro–Wilk test was used to test the normal distribution of variables. Categorical variables were reported as numbers and percentages. The differences in the variables were tested using χ^2, ANOVA, or Kruskal–Wallis tests, followed by *post-hoc* analysis using Tukey's or Dunn's test, as appropriate. *P*-values <0.05 were considered statistically significant. Spearman

Table 1. Patient characteristics with regard to antiplatelet regimen

Variable	Total (n = 119)	ASA only (n = 74, 62.2%)	ASA + clopidogrel (n = 24, 20.2%)	ASA + ticagrelor/prasugrel (n = 21, 17.6%)	*P*-value
Age, years	68 (59–72)	68 (59–74)	69 (65–72)	61 (56–69)	0.12
BMI, kg/m^2	27.7 (25.0–31.0)	28.4 (24.9–31.2)	27.0 (25.2–31.1)	26.5 (25.3–29.4)	0.85
Men, n (%)	87 (73.1)	56 (75.7)	16 (66.7)	15 (71.4)	0.68
Clinical variables, n (%)					
Hypertension	113 (95.0)	69 (93.2)	23 (95.8)	21 (100)	0.27
Dyslipidemia	111 (93.3)	69 (93.2)	21 (87.5)	21 (100)	0.14
Diabetes	47 (39.5)	26 (35.1)	13 (54.2)	8 (38.1)	0.26
Current smoking	29 (24.4)	17 (23.0)	5 (20.8)	7 (33.3)	0.58
Family history of CAD	32 (26.9)	25 (33.8)	4 (16.7)	3 (14.3)	0.08
Prior MI	59 (49.6)	24 (32.4)	17 (70.8)	18 (85.7)	**<0.001**
Prior PCI	69 (58.0)	35 (47.3)	16 (66.7)	18 (85.7)	**0.003**
Prior stroke/TIA	13 (10.9)	7 (9.5)	4 (16.7)	2 (9.5)	0.63
Multivessel disease	67 (56.3)	38 (51.4)	15 (62.5)	14 (66.7)	0.18
Pharmacotherapy, n (%)					
Beta-blocker	105 (88.2)	62 (86.1)	23 (95.8)	20 (95.2)	0.26
ACE-I/ARB	103 (86.6)	64 (88.9)	20 (83.3)	19 (90.5)	0.71
Statin	107 (89.9)	63 (86.3)	23 (95.8)	21 (100)	0.10
Insulin	14 (11.8)	5 (6.9)	6 (25)	3 (14.3)	0.06
Laboratory parameters					
hs-CRP, mg/l	1.4 (0.8–2.9)	1.2 (0.7–2.2)	1.4 (1.0–4.3)	3.0 (1.4–4.5)	**0.03**
White blood count, 10^3/µl	7.6 (5.9–8.9)	7.6 (6.4–8.7)	7.0 (5.7–8.7)	8.6 (5.90–9.3)	0.28
Hemoglobin, g/dl	13.9 (12.9–14.7)	14.1 (31.1–14.9)	13.6 (12.4–14.7)	13.1 (12.4–14.0)	0.054
Platelet count 10^3/µl	226 (196–264)	220 (185–252)	231 (198–274)	255 (217–299)	0.07
Mean platelet volume, fl	10.3 (9.8–11.0)	10.3 (9.9–11.2)	10.3 (9.8–10.9)	10.5 (10.0–10.9)	0.78
Glomerular filtration rate, ml/min/1.73 m^2	75 (58–87)	75 (58–88)	67 (56–78)	77 (63–90)	0.15
LDL cholesterol, mmol/l	2.1 (1.6–2.8)	2.2 (1.9–3.0)	1.7 (1.4–2.3)	2.3 (1.4–2.8)	**0.029**
HbA1c, %	5.9 (5.7–6.5)	5.9 (5.6–6.4)	6.3 (5.8–8.0)	5.8 (5.7–6.2)	0.10
Platelet activation and fibrinolysis parameters					
sCD40L, ng/ml	1.1 (0.8–1.7)	1.2 (0.9–1.8)	1.2 (0.9–1.9)	0.8 (0.6–0.9)	**0.001**
P-selectin, ng/ml	60.7 (48.0–80.1)	64.9 (53.7–82.7)	57.9 (49.1–80.8)	46.4 (36.0–61.4)	**0.005**
Platelet factor 4, ng/ml	427 (247–769)	539 (300–895)	357 (242–569)	325 (197–623)	0.060
PAI-1, ng/ml	27.4 (19.4–39.9)	29.1(20.0–42.4)	31.7 (22.3–47.5)	18.0 (16.6–26.6)	**0.008**

P-values in *post-hoc* tests for:
hs-CRP: ASA vs. ASA+ticagrelor/prasugrel ($P = 0.028$); LDL-C: ASA vs. ASA + clopidogrel ($P = 0.023$), ASA + clopidogrel vs. ASA + ticagrelor/prasugrel ($P = 0.013$); sCD40L: ASA vs. ASA+ticagrelor/prasugrel ($P = 0.001$), ASA+clopidogrel vs. ASA+ticagrelor/prasugrel ($P = 0.005$); P-selectin: ASA vs. ASA + ticagrelor/prasugrel ($P = 0.004$); PAI-1: ASA vs. ASA+ticagrelor/prasugrel ($P = 0.029$), ASA + clopidogrel vs. ASA + ticagrelor/prasugrel ($P = 0.008$)

Abbreviations: ACE-I/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; ASA, acetylsalicylic acid; BMI, body mass index; CAD, coronary artery disease; HbA1c, glycated hemoglobin; hs-CRP, high-sensitive C-reactive protein; LDL, low-density lipoprotein; MI, myocardial infarction; PAI-1, plasminogen activator inhibitor-1; PCI, percutaneous coronary intervention; sCD40L, soluble CD40 ligand; TIA, transient ischemic attack

correlations were calculated, and scatterplots were used for graphical representation. Analyses were performed using IBM Corp. software released in 2021 (IBM SPSS Statistics for Windows; version 28.0.; IBM Corp, Armonk, NY, US).

RESULTS AND DISCUSSION

We enrolled 119 patients (median age 68 [59–72] years; 73.1% men), including 74 (62.2%) on ASA monotherapy, 24 (20.2%) on ASA plus clopidogrel, and 21 (17.6%) on ASA plus ticagrelor/prasugrel (Table 1). The three subgroups shared similar demographic and clinical profiles except for prior ACS and PCI, which were more prevalent in the groups on DAPT. Basic laboratory parameters were similar, regardless of antiplatelet regimen, except for C-reactive protein (CRP), which was higher in patients on ASA plus ticagrelor/prasugrel as compared with ASA only. LDL-cholesterol was lower in the ASA plus clopidogrel patients as compared with the remaining groups (Table 1).

Among platelet activation markers, patients on ASA plus ticagrelor/prasugrel had 33.3% lower sCD40L as compared to the remaining groups, while P-selectin was 28.5% lower compared with the ASA group (Table 1). sCD40L was higher in patients with diabetes and multivessel disease; P-selectin was associated with obesity and diabetes (Supplementary material, *Table S1*). In line, sCD40L and P-selectin correlated positively with glycated hemoglobin (HbA1c, Supplementary material, *Table S1*), which agrees with previous reports [8].

In the ASA plus ticagrelor/prasugrel group, PAI-1 was 38.1% and 43.2% lower as compared with the ASA plus clopidogrel and ASA monotherapy groups (18.0 [16.6–26.6] vs. 29.1 [20.0–42.4] vs. 31.7 [22.3–47.5] ng/ml, respectively, $P = 0.008$). As expected, PAI-1 was higher in women, patients with obesity, hypertension, and diabetes (Supplementary material, *Table S2*). There were positive correlations between PAI-1 and platelet markers, along with body mass

index (BMI), lymphocyte and platelet counts, and HbA1c (Supplementary material, *Table S1*).

To our knowledge, this is the first study to show that ticagrelor/prasugrel-based DAPT is associated with lower sCD40L levels in CCS patients. In a trial comparing DAPT with clopidogrel 75 mg vs. ticagrelor 90 mg bid vs. ticagrelor 180 mg bid in ACS [9], the therapies had no effect on sCD40L levels, which were much higher as compared to the values in our study (5.0 [2.7–7.1] vs. 1.1 [0.8–1.7] ng/ml). In CCS, the impact of these inhibitors appears stronger and may be beneficial in secondary prevention.

We observed lower P-selectin in patients treated with ASA plus ticagrelor/prasugrel vs. ASA monotherapy. In 126 ACS survivors, lower P-selectin was reported in patients treated with ticagrelor vs. clopidogrel, as part of the DAPT regimen [5].

A novel finding is that CCS patients on ticagrelor/prasugrel have reduced plasma PAI-1, the key modulator of fibrinolysis despite similar demographic and clinical characteristics. Ticagrelor has been shown to decrease the expression and activity of PAI-1 in activated endocardial cells in patients with atrial fibrillation [10]. Reddel et al. [11] reported hypofibrinolysis with elevated PAI-1 in CCS as compared to healthy volunteers, with PAI-1 levels similar to the ones in our cohort, without any effect of the antiplatelet regimen. However, their study included 56 CCS patients without subjects on ticagrelor or prasugrel [11]. In another study of 60 CAD patients, cangrelor, but not ticagrelor, reduced clot lysis time [12]. Since most circulating PAI-1 comes from platelet α-granules and is released upon platelet activation [13], a positive correlation between PAI-1 and P-selectin in our study might indicate that lower PAI-1 concentrations result from platelet inhibition under the ASA plus ticagrelor/prasugrel regimen. Mechanisms behind PAI-1 suppression by ticagrelor or prasugrel require further investigation.

The fact that sCD40L was lower while CRP was higher in the group taking ASA plus ticagrelor/prasugrel deserves a comment. sCD40L exerts prothrombotic and inflammatory effects. This mechanism may gain significance in ACS, when platelet activation is fulminant, resulting in a correlation between sCD40L and CRP. In CCS, other factors, such as oxidized lipids or reactive oxygen species, drive chronic inflammation [14]. Due to an abundance of such up-regulators in an atherogenic milieu, CRP levels may be high despite attenuated sCD40L.

The study has several limitations. The cohort was relatively small, especially regarding the subgroups on DAPT, without a possibility to compare ticagrelor (n = 16) with prasugrel (n = 5); therefore, the results should be treated as preliminary. We did not assess clot lysis time to show the impact of PAI-1 on fibrinolysis which is suppressed in CCS [15]. Clinical outcomes during follow-up were beyond the study protocol.

In conclusion, in advanced CCS, treatment with ticagrelor/prasugrel combined with ASA may reduce not only platelet activation but also plasma PAI-1 as compared with ASA monotherapy or ASA plus clopidogrel. Our results suggest potential additional benefits from P2Y12 receptor inhibition, namely improved fibrinolytic capacity, which might contribute to lowering the risk of thrombotic events.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

Conflict of interest: None declared.

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